FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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MEMORANDUM

DATE: August 12, 2003

TO: Chair, Members and Invited Guests

FROM: Bob A. Rappaport, M.D.
Director, Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

RE: Overview of the September 9 and 10, 2003 meeting of the Anesthetic and Life Support Drugs Advisory Committee to discuss risk management plans for extended-release opiate analgesic drug products

Throughout modern history, public opinion regarding the opiates has cycled between viewing them as an essential medical treatment and viewing them as a public health menace. Only in the last few decades has the medical community attempted to achieve a balanced view of opiates through careful, evidence-based investigation. Twenty-years ago, it was accepted dogma in medical training that opiate analgesics should only be used on an "as needed" basis for acute pain. Opiates for chronic pain were used only for the most intractable of cases, usually those patients in the terminal stages of cancer. The fear that patients with chronic pain would become addicted was often fueled by a lack of understanding of the physiological tolerance that occurs with these drugs. Today, opiate analgesics are among the most widely prescribed drug products in the medical armamentarium. Chronic pain is aggressively treated, and opiates have become a mainstay of that treatment.

The problems of abuse and addiction have not diminished, however, in spite of our greater understanding of the pharmacodynamics of opiate analgesics. In fact, prescription opioid analgesic abuse has been increasing at an alarming rate over the past few years. The consequences of this increase have been amply chronicled in both the medical literature and the national press. Entire communities in some rural sections of the country

have been impacted by widespread diversion, abuse and addiction. Many young people have reportedly died as a result of experimention with the recreational use of opioid analgesic drug products, particularly extended-release dosage forms. These extended-release products are also of particular interest to the hard-core drug abusers and to the criminal elements that profit from them. The high street price that dealers get with prescription opiates has led to a rash of pharmacy thefts, prescription mills and violent crimes.

Additional issues have arisen with the proper management of these products in medical practice. With broader use, there appears to be less depth of understanding about these drugs among some of the physicians who now prescribe them. The modified-release opiates, while offering greater ease of use for patients, have inherent risks due to the availablity of high-dose unit-of-use products. Long-acting opiates recently entering into the pain-treatment arena, such as methadone, have pharmacokinetic and pharmacodynamic properties that may result in significant morbidity in the hands of inexperienced prescribers. Chronic opiate therapy often requires that patients be cycled from one opiate to another in order to maximize efficacy and minimize side effects. Limited data to support proper dosing during conversion from one opiate to another result in a need to rely upon clinical experience to avoid unacceptable levels of either over- or under-dosing.

The number of Americans who suffer from chronic pain is estimated to be in the tens of millions. Many of those patients will receive treatment with opiate analgesics. Physicians with specific expertise in pain management are limited in number and availability. Thus, the challenge becomes how the medical community can continue to provide access to patients who appropriate candidates for treatment with prescription opiates, while limiting the misuse, abuse and diversion of these products.

The development of risk management strategies to prevent the inherent negative effects associated with approved drugs remains a high priority for the Agency. Risk management plans have been developed and implemented for a number of drug products that have received Agency approval over the past few years. Included in these recent approvals are some of the opiate analgesics. New risk management strategies are currently under development by industry. It is essential for the new drug review divisions that evaluate opiate analgesic marketing applications, in concert with the Agency's Controlled Substance Staff and Office of Drug Safety, to provide sound and consistent, evidence-based advice regarding the risk management of those products. Not only must we clearly understand the effectiveness of these plans, we must also be able to assess any negative outcomes resulting from their implementation.

The first day of this Advisory Committee meeting will include presentations on the current use of opioids in medical practice and the status of their misuse and abuse, both within legitimate medical practice and in the criminal setting. Existing risk management plans for opiate analgesics and for other drug products will be reviewed. Particular attention will be paid to the individual risk management "tools" that have been included

in these previous plans to assess the various domains of risk that exist for different drug classes. Data will be presented to define the extent of the underlying problem of misuse and abuse. Data, however, on the actual performance to date of risk management plans (on the effectiveness of the plans and any unintended consequences) are limited. For this reason, we have assembled a committee that includes some of the leading experts in the fields of pain treatment, addiction treatment and epidemiology, and risk management.

The second day of this meeting will focus on a specific risk management proposal that is currently under review by the Division. Palladone, a modified-release formulation of hydromorphone, has been developed by Purdue Pharma L.P. for the treatment of opioid-tolerant patients with chronic pain. The efficacy of this drug when used for its intended purpose is not in question at this meeting. Rather, the Committee will be asked to assess the Palladone risk management plan and to provide the Division with guidance that will allow us to identify any potential improvements. The Committee will also be asked to suggest appropriate methodologies for helping to assess the effectiveness of this and future risk management plans.

This briefing package provides background information that we hope you will find useful in preparation for this meeting. Included in this package are materials describing the strengths and weaknesses associated with the various databases that have been used to prepare some of the Agency presentations. Reference documents that provide a backdrop for our presentations on the use and misuse of opiate analgesics have also been included. There are examples of individual risk management tools (e.g. prescription monitoring programs) and of risk management plans for approved products. While the two plans that have been included do not specifically address the risks associated with extended-release opiate analgesics, they do exemplify some of the same features that might be included in an opiate analgesic risk management program. In addition, we have included a copy of the Agency's recent concept paper on risk management programs.

In our mission to bring safe and effective analgesic drug products to the American public, it is of paramount importance that we strike a reasonable balance between providing needed medications to the millions of patients who suffer from chronic pain (many of whom have been undertreated historically) and limiting the misuse and abuse of those medications. The Agency will best achieve a positive outcome by working in concert and understanding the viewpoint of other government agencies, including DEA, of experts in pain and experts in addiction treatment, and of patients and their families, as well as the public at large. We sincerely hope that each of these stakeholders in this effort are prepared to share in the task before us.